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INO IN PREMATURE NEWBORNS – SHORT AND LONG TERM OUTCOME

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ABSTRACT

According to a rising number of randomized controlled clinical trials the "off label" usage of iNO in premature babies is rising in the last few years. Nowadays in the era of the precise medicine it is of great importance to differentiate the population of premature babies with critical hypoxic pulmonary failure that is most likely to gain positive effect from iNO treatment. The described trial compares the iNO therapy with the conventional therapy regarding the short and long term outcome in premature newborns below 30 week of gestation. A group of premature infants with specific characteristics is clearly defined, where the usage of iNO leads to positive effect concerning the outcome.

KEY WORDS: iNO, ELBW, Pulmonary hypertension, Bronchopulmonary dysplasia, chronic complications.

INTRODUCTION:
Based on data from most of the clinical trials, concerning usage of inhaled nitric oxide (iNO) in infants below 34 weeks of gestation (w.g.), the drug could be used in three groups premature newborns [1]:

- In the first three days of life in infants with high Oxygenation index (OI) – the so called „rescue" therapy
- Routinely in all infants on mechanical ventilation – the so called „prophylactic" therapy
- Late usage when the risk for Bronchopulmonary dysplasia (BPD) is high – the so called „BPD prevention" therapy.

Evaluation of the Pulmonary hypertension (PH) and the treatment effect is often very hard and incorrect in premature babies. Echocardiography is a method of choice. One group of premature infants is approved to have the greatest treatment benefit, receiving iNO for Hypoxic pulmonary failure (HPF) and/or PH. This group received corticosteroid prophylaxis prenatally and had a better effect than infants without prophylaxis. Recently the American Heart Association and the American Thoracic Society stated in their pediatric PH protocols [2]: „iNO could have positive effect in premature infants with severe hypoxemia, which is a result from Persistent pulmonary hypertension of the newborn (PPHN)–physiology, especially if the hypoxemia is connected with Preterm premature rupture of membranes (PPRM) and oligohydramnion".

The huge number of randomized clinical trials and meta analyses do not clarify the role of iNO usage in premature infants. The ambivalent data, the lack of consensus regarding the dose, the most favorable time of delivery, the most likely group of premature infants that could have benefit from the treatment, are the needed prerequisite for the following trial.

Patients and methods /Table 1/:
The patients from the trial are divided in two groups, according to the treatment method that is provided:

iNO group – 11 infants /34.4%/:
Premature newborns below 30 week of gestation with extremely low birth weight in critical condition, that are still on mechanical ventilation seven days after they received Surfactant. Therapy with iNO starts after echocardiography for ruling out cardiac malformation, persistent ductus arteriosus and cardiac failure. The parents of the enrolled babies sign an informed concern before initiation of treatment.

Control group – 21 infants /65.6%/:
A retrospective study of extremely low birth weight (ELBW) infants in critical condition that receive only optimal mechanical ventilation after they had Surfactant.

Concerning the gestational age and weight there is no difference with statistic significant difference between the groups: the mean gestational age in the iNO group is 27±1 weeks, while in the control group is 26±2 weeks. The mean weight in the iNO group is 709±202g, while in the control group is 699±148g.

The infants from the iNO group have statistic significant lower mean value of pH from the umbilical artery than the control group (p-0.026).

Concerning the main complications of pregnancy, there are two conditions that are statistic different in the two groups. Preeclampsia and/or hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome are more common in the iNO group (p-0.011), while PPRM and oligohydramnion are more frequent in the control group (p-0.014). There is no difference between the groups in regard to the other complications of pregnancy.

Table 1: Perinatal characteristics of infants

Characteristic*	iNO gr./ n=11/	Control gr. /n=21/	P
Weight (g)	709 (410-1040)	699 (490-1040)	0.874
Gestational age (w.g.)	27 (24-28)	26 (24-30)	0.455
Male, n (%)	6 (55)	12 (57)	0.590
IUGR, n (%)	5 (45)	10 (48)	0.602
Apgar score, 1 min.	<5 (1-4)	<5 (1-6)	0.760
Apgar score, 5 min.	<7 (3-7)	<7 (1-7)	0.744
pH	7.23 (7.09-7.31)	7.31 (7.10-7.50)	0.026
PPRM, n(%), oligohydramnion	2 (18)	10 (48)	0.014
Preeclampsia, HELLP	8 (73)	8 (38)	0.011
Multiple pregnancy	3 (27)	7 (33)	0.628
Maternal-fetal infection	2 (18)	4 (19)	0.892
Caesarean section, n (%)	10 (91)	12 (58)	0.017
Corticosteroid prophylaxis	8 (73)	10 (48)	0.266

IUGR – intrauterine growth retardation; PPRM - preterm premature rupture of membranes; HELLP – hemolysis, elevated liver enzymes, and a low platelet count

** Data are presented as an average value within range in brackets or as a number and % (in brackets)*

RESULTS AND DISCUSSION:
The first assessment of the PH is done in the first two weeks after birth. This PH is called "early" PH. The next assessment for the so called "late" PH is done in the 36 week of gestation in all the patients from the trial, no matter if they have or what is the severity of their BPD /figure 1/.

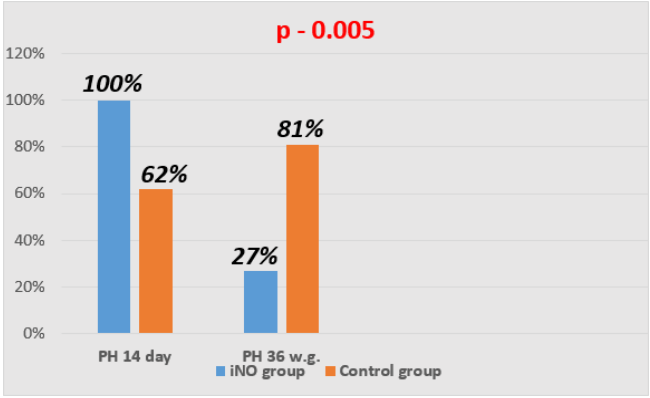

Figure 1. PH in the two groups, found using echocardiography

PH – pulmonary hypertension

In the iNO group 100% of the children have "early" PH, found on the echocardiography exam in the first 14 days of life, while in the control group 62% of the newborns show signs of "early" PH. Data that all newborns in the iNO group have "early" PH is a negative predictive sign for late development of BPD and the corresponding "late" PH. iNO therapy in this group is truly reasonable in order to prevent the anticipated late complications.

Analysis of the data from the 36 week of gestation shows different results. "Late" PH is found in only 27% of the babies in the iNO group, which means that we have 73% reduction of the morbidity. A quite detailed analysis shows that this 27% of the patients have the following characteristics: male gender, < 26 w.g., delivered after pregnancies complicated with severe preeclampsia and IUGR. In the control group 81% of the patients have "late" PH, which value is more than the early screening value (62%).

Concerning "late" PH there is statistic significant difference between both groups (p – 0.005). This result is of great importance, because points out that treating ELBW infants in critical condition and data for "early" PH with iNO can lead to significant reduction of the frequency of PH in 36 w.g. This is connected with reduction of the risk for development of long term pulmonary complications, that always accompany PH.

The newborns in our clinical trial are actually the most likely group that can develop PH – ELBW infants, with IUGR, born after complicated pregnancies (PPRM and severe preeclampsia). Concerning the risk factors our results do not differ from the ones, described in the literature [3,4].

Characteristic for the short term effect of treatment with iNO is the evaluation of the duration of artificial (mechanical) ventilation, the duration of oxygen therapy, duration of hospital stay and the frequency of unfavorable outcome (lethal outcome). The first clinical trials for iNO in premature babies started to seek the answers of these questions [5,6]. The results from all the trials show that there is no difference between the iNO groups and the control groups in regard to the short term outcome. Our results are represented on Table 2.

Table 2: Analysis of the short term outcome of the therapy

Characteristic*	iNO gr. / n=11/	Control gr. /n=21/	P
Lethal outcome, n(%)	2 (18)	3 (14)	1.000
Hospital stay (days)	107±31	108±48	0.961
M.V. (days) O_2 (days)	68±37 25±11	39±22 72±18	0.037 0.000

M.V. – mechanical ventilation; O_2 – oxygen therapy;

** Data are presented as an average value within range or as a number and % (in brackets)*

The treatment of ELBW infants in Neonatal intensive care units (NICUs) is one of the most long lasting and expensive. This group of patients has a lot of specific problems and complications, connected mainly with the extreme prematurity of all the organs and systems, as well as with the total luck of mechanisms for adaptation to the extrauterine way of life. As can be noticed from the conducted trial, one new medicine like iNO can not change such complex parameters like duration of hospital stay and lethal outcome.

Our data show that iNO alone can not change the duration of the mechanical ventilation, which is dependent on a lot of factors. The main duration of the oxygen therapy in the iNO group (25 days) is less than that in the control group (72) and between the two groups there is a statistic significant difference with p-0.000.

In conclusion, the analysis of the data, concerning the short term outcome in ELBW infants treated with iNO, shows that our results do not differ from the cited results in literature [6,7]. The favorable effect of the medicine on the duration of the oxygen therapy could be connected with a lesser degree of severity of the long term complications, characteristic for the premature infants.

The long term outcome in premature infants treated with iNO is evaluated and the following morbidities are analyzed: BPD, Retinopathy of prematurity and brain change, seen on ultrasound examination.

In the iNO group 9% of the patients have no BPD and there is a statistic significant difference between the two groups with p–0.002. In the therapeutic group 1/3 of the babies have mild degree BPD, while in the control group are found no patients with mild degree and this is very important difference with p–0.009. In regard to the moderate and severe degree of BPD we find no difference between the groups with p-0.441 and 0.472 respectively. When analyzing the patients with no or with mild BPD we find that these babies have the following characteristic features:

- Gestational age ≥ 27 w.g.
- Female gender
- PPRM and completed corticosteroid prophylaxis before birth
- Echocardiographic data for „early" PH, no data for „late" PH.

The positive effect of iNO in regard to the frequency and the severity of BPD is most possibly connected with the reduction of the "early" PH in the most favorable group of patients – the ones with PPRM, comparatively higher gestational age and completed corticosteroid prophylaxis.

In the control group 38% of the patients and 27% in the iNO group have different degrees of Retinopathy of prematurity. Between the groups there is no difference with p – 0.703. iNO do not change the frequency of this chronic disease in the premature infants, no matter that the medicine has effect on the duration of the oxygen therapy and mechanical ventilation.

We find no statistic significant difference between the groups in regard to the brain changes seen on ultrasound examination in 36 gestational week. Typical are different degrees of intraventricular hemorrhages. From the severe morbidities we find hydrocephalus in 9% in the iNO group and periventricular leukomalacia in 11% in the control group.

CONCLUSION:

According to the data from a number of clinical trials the "off-label" usage of iNO in different groups of premature infants continues and a tendency for more frequent usage is also observed [8,9]. The explanation of this fact is connected with the desire of the neonatologists to find an opportunity for a greater survival of extremely premature infants with minimal long term complications.

In the era of the current precise medicine it is of great importance to find out this group of premature infants with critic hypoxic pulmonary failure that is most likely to have positive effect being treated with iNO [10].

Premature infants with PPRM and completed corticosteroid prophylaxis before birth (the so called "forth group" premature infants treated with iNO), that have severe hypoxemia as a result from Persistent pulmonary hypertension of the newborn (PPHN), have the same positive effect from the medicine like mature infants with PPHN. Exactly this group of premature patients is most likely to have positive effect from the pulmonary vasodilator, applied during the first 28 days of life [11].

The current clinical trial emphasizes on the positive effect of iNO in regard to the PH in premature babies. Our results show that 73% of the infants in the therapeutic group have effect from treatment, as well as a statistic significant difference between the groups. Infants, that are most likely to have positive effect have the following characteristics:

- Gestational age > 26 w.g.
- Female gender.
- Echocardiography performed during the first two weeks after birth with data for "early" PH.
- Premature babies with no IUGR and no history of preeclampsia of the mother.
- Premature babies, born from pregnancies complicated with PPRM.
- Completed one course of antenatal corticosteroids prenatally.

In regard to the long term outcome we find that treating premature infants below 30 w.g. with iNO do not change such complex parameters like duration of hospital stay and lethal outcome. Nevertheless therapy with iNO increases the percent of patients that survive with mild or with no BPD.

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